Center for Devices and Radiological Health

September 1997

Medical Glove Powder Report

(38)

Issue

Do current Center policies adequately address potential adverse health effects of medical glove powder?

Background

The Food and Drug Administration (FDA), as well as other state and federal agencies, has received requests to ban the use of glove powder. It has been suggested that experimental and clinical studies demonstrate that glove powder on medical gloves can enhance foreign body reactions, increase infections and act as a carrier of natural latex allergens. The National Institute of Occupational Safety and Health (NIOSH) recently issued a safety alert recommending the use of powder-free, reduced protein content latex gloves to reduce exposure to natural latex proteins (allergens).

For the purposes of this document, total particulate matter [glove powder] includes dusting or donning powders, mold-release compounds, and manufacturing debris. Dry lubricants such as cornstarch, silicone etc., are used to make donning gloves easier and to prevent gloves from sticking together during the manufacturing process. Cornstarch, which meets the specification for absorbable dusting powder in the United States Pharmacopoeia (USP), is the most common lubricant for patient examination gloves. Only absorbable dusting powders that have an approved Premarket Approval Application (PMA) or New Drug Application (NDA) may be used for lubricating surgeons gloves. There are no comprehensive studies of the amount of absorbable dusting powder used on powdered gloves. It is estimated that amounts of total particulates may range from 120 to 400 mg for a medium size powdered glove. [Appendix A]

Glove powder is composed of particles, thus, issues related to biologic responses to foreign bodies apply to both natural rubber latex (NRL) and synthetic gloves. Industry conversion from talcum powder, a non-absorbable lubricant, to absorbable cornstarch has greatly reduced the formation of granulomas. Adhesions of peritoneal tissue after surgery are associated with foreign bodies and remain a concern. The issue of the level of microorganisms (bioburden) on gloves has been raised under various circumstances. However, evidence that bioburden and powder are related do not exist at this time. [Appendix B]

Experimental and clinical data demonstrate that: natural latex proteins are allergenic, natural latex proteins bind to cornstarch, aerosolized powder on NRL gloves is allergenic and can cause respiratory allergic reactions. These published studies support the conclusion that airborne glove powder represents a threat to individuals allergic to natural rubber latex and may represent an important agent for sensitizing non-allergic individuals. There are also published data (although limited) and clinical experience that cornstarch powder on NRL gloves may also be a contributing factor in the development of irritation and Type IV allergy. [Appendix B]

There are alternatives to dusting powder for lubricating natural rubber latex surfaces. The most common method is chlorination. Chlorine reacts with the natural rubber latex surface to reduce the natural tackiness, eliminating the need for adding dusting powder. The extra washing performed during the chlorination process provides an added benefit by also greatly reducing the level of soluble natural latex proteins. However, chlorination affects some of the mechanical and physical properties. Gloves made from alternative materials, not containing natural allergens, are available, but none possess the unique mix of properties offered by natural rubber latex. [Appendix C]

Market availability must be factored into any policy decision regarding medical glove powder. The large majority of medical gloves used in the U.S. are imported. In 1996, 20.8 billion medical gloves were imported into the U.S.: 90% natural rubber latex and 10% nonlatex. Of the 90% that were natural rubber latex, 20–25% were powder-free and chlorinated. Only a small number of manufacturers are using a process other than chlorination to produce powder-tree gloves. A rapid increase in the demand for non-powdered gloves could result in products with poor barrier integrity and/or unacceptable shelf life entering the U.S. market. In addition to concerns about glove quality, most alternatives to glove powder currently would entail substantially increased costs to the U.S. health care system. [Appendix D]

Conclusions

(1) The major adverse impact of glove powder appears to be its contributing role in natural rubber latex allergies.

(2) Glove powder acts as an airborne carrier of natural latex proteins.

(3) Exposure to airborne natural rubber latex allergens can be most effectively reduced by considering both the level of natural latex proteins and the amount of glove powder on medical gloves.

Options

Immediately banning the use of glove powder would cause a market shortage that could result in inferior products and increased costs. Doing nothing to address the problem of airborne allergens which are carried by glove powder, would appear to be an abrogation of FDA's responsibility to protect public health. It appears that neither extreme offers a viable option. The following options are offered for consideration:

1. **Provide adequate information for the consumer to make an informed decision.** Require that the amount of water-soluble natural latex proteins and the amount of particulate present on powdered gloves be stated on the product label. In addition, establish upper limits for the amount of water-soluble natural latex proteins and glove powder allowed.

   Pro:

   - Should not precipitate market shortage.
   - Labeling requirement is achievable using current ASTM standard protocols.
   - Market forces may lower both water-soluble protein and particulate levels.

   Con:

   - Upper limits for water-soluble protein and particulates have to be established based on state-of-technology considerations.
   - Labeling requirement would not be effective without education effort by industry and/or the FDA.
   - Would require a new regulation.

2. **Ban powdered medical gloves at some predetermined time in the future.** Require manufacturers to convert to powder-free production or provide safety data, including foreign body and airborne allergen concerns, by a certain date.

   Pro:

   - Should not precipitate market shortage.
   - Requires no education effort
   - Offers a greater degree of protection from airborne natural latex allergens than Option

- Offers a greater degree of protection from airborne natural latex allergens than Option 1.

Con:

- Conversion date would have to be negotiated with industry to avoid market shortage.
- The effect of powder-free gloves on user preferences and needs for qualities such as tactile sensation, etc. are largely unknown.
- Would most likely result in increased costs to the U.S. health care system.
- It is not clear that the amount of particulates need to be reduced to the "powder-free" level in order to offer an acceptable level of protection from adverse health effects. Does not address natural latex protein level.
- Would require a new regulation.

Author: Mel Stratmeyer

Recommendations

These recommendations represent activities either currently ongoing or which could be initiated. Detailed action plans required to accomplish these recommendations are not addressed in this document, but will need to be developed.

Glove Powder

1. Establish a maximum allowable powder level to reduce the amount of powder on powdered medical gloves by working with ASTM. *
2. Standardize the maximum allowable amount of powder on powder-tree medical gloves by working with ASTM. *
3. Adopt the use of an accepted gravimetric method (such as ASTM D 6124-97) to measure total powder to demonstrate powder-free content claims
4. Ran medical gloves that contain talc and/or lycopodium.

Protein

5. Reduce the level of water-soluble protein on finished medical gloves by working with ASTM to establish a maximum allowable glove protein level. *

Barrier Properties

6. Define effects of processing, handling, and environment on the long-term barrier characteristics of all medical gloves (natural rubber latex and alternative materials). Establish shelf-life requirements.
7. Promote the use of Process Controls, as described in the Quality System Regulation, for controlling manufacturing processes, such as chlorination, to minimize adverse effects on glove properties.

Labeling

8. Require manufacturers to label all medical gloves with the following additional information:
   a. the total quantity of glove powder content, unless the manufacturer has demonstrated by means of an accepted gravimetric method that the total powder is 2 mg or less;
   b. the total quantity of remaining water-soluble protein; and
   c. an expiration date as determined by shelf-life requirements.
9. Explore the possible need to include glove powder content labeling on all product labels.

* In addition to ASTM, work with other voluntary standards organizations when appropriate.

Appendix A

Glove Powder Background

History

Since the introduction of surgical gloves to the operating theater in 1889, various types of lubricating materials have been used to aid in glove donning. These range from various wetting techniques to the use of dusting powders such as a mixtures of Lycopodium spores and talc, talcum powder alone, calcium carbonate, and different types of starch products. The first lubricant used was a powder made of Lycopodium spores (ground pines or club moss). This lubricant was quickly accepted and was used worldwide until the 1930's, when surgeons realized that it caused granuloma and adhesion formation. Lycopodium was toxic and became unacceptable for use as a glove lubricant As a result, talcum powder (hydrous magnesium silicate), a non-absorbable lubricant, was introduced as a replacement for Lycopodium spores. In the 1940's talcum powder was also identified as a cause of post-operative complications such as granuloma and adhesion formation. In 1947 a modified cornstarch glove powder was introduced to the medical community as an absorbable and non-irritating powder. By the early 70's, many surgical glove manufacturers replaced talc with the modified cornstarch.

Cornstarch, which is absorbable through biological degradation, that meets the specification for absorbable dusting or dusting powder in the United States Pharmacopoeia (USP) is the most common lubricant for patient examination gloves. The absorbable dusting powder used on medical gloves is a chemically cross-linked cornstarch to which no more than 2% of magnesium oxide is mixed to prevent caking or turning to paste. Talc, cotton flock, and other non-absorbable materials are not acceptable as a lubricating, dusting or donning powder. ASTM* D 3578-95 (Standard Specification for Rubber Examination Gloves), D 5250-92 (Standard Specification for Polyvinyl Chloride Gloves for Medical Application) and ASTM
D 3577-91 (Standard Specification for Rubber Surgical Gloves) require the inside and outside surfaces of medical gloves to be free of talc.

In addition to dusting powder, other lubricants may also be used in the manufacturing process. Latex and some polymers are tacky and gloves made of these materials stick to the mold or former. A mold-release lubricant such as calcium carbonate or a mixture of calcium carbonate and cornstarch is used to enable the removal of gloves from molds. The other side of the glove may be coated with a donning lubricant, such as cornstarch or silicone, to make donning gloves easier and to prevent gloves from sticking during the manufacturing process.

Over the past three years, FDA has received requests to ban the use of all glove powders. These requests have been based on repeated clinical and experimental studies reporting that cornstarch on surgical gloves can damage tissue's resistance to infection, enhance the development of infection, serve as a potential source of occupational asthma, and provide a source of natural latex protein exposure to natural latex allergic individuals. The issues regarding the use of glove powder, except for the transport of natural latex protein allergens, apply to the use of glove powder on both natural rubber latex and synthetic gloves.

As a result of continuing concern over adverse reactions to cornstarch, in 1971 FDA required manufacturers to place a warning label on the glove packages. The warning label stated, "CAUTION: After donning, remove powder by wiping gloves thoroughly with a sterile wet sponge, sterile wet towel, or other effective method." Studies have shown that efforts to remove the cornstarch from the surgical gloves using washbasins and wet cloths are unsuccessful. It has been reported that such efforts have led to added clumping, creating even less absorbable aggregates.

Because of multiple concerns about the adverse health effects of all particulate matter from the surface of medical gloves (Appendix B), there is a recognized need for "low powder" and "powder-free" glove products. Particulates found on the gloves can include dusting powder, mold- or former-release compounds, lint, dust, colloidal solids, cotton, cellulose, wood fibers, metal, paper particles from packaging, and manufacturing debris. The most common particulates on gloves are dusting powder and former-release compounds added by manufacturers. Gloves with sufficiently low amounts of residual particulates are referred to as "powder-free", or "powderless." Several brands of powder-free examination and surgical gloves have been developed, some using powder-free manufacturing processes. Gloves labeled as "powder-free" may be coated with a polymer or added powder may have been removed through washing and chlorination. Although gloves are labeled as "powder-free", they contain various amounts of powder or particulates matter. FDA has adopted 2 milligrams particulate weight (based on the ASTM test standard D 6124-97) per glove powder or less as a basis for approving powder-free gloves. Alternatively, the Office of Device Evaluation (ODE) has accepted a negative iodine test to support "powder-tree" claims. However, virtually all glove manufacturers provide particulate weight. For comparison purposes, a medium size powdered glove, depending on the pmcessing, contains about 120400 milligrams of residual debris, former-release and dusting powder.

Problems associated with the use of powder-free examination and surgical gloves include concerns about the particulate levels remaining on the gloves, use of chlorination, and the treatment with other chemical agents that may have a deleterious effect on the physical properties and/or performance of the gloves.

Sureeon's Gloves

Surgeon's gloves, defined as "a device made of natural or synthetic rubber intended to be worn by operating room personnel to protect a surgical wound from contamination . . ." are classified as Class I medical devices under 21 CFR 878.4460.

Absorbable dusting powder for lubricating a surgeon's glove is classified by the FDA General and Plastic Surgery panel under 21 CFR Part 878.4480 as a class III device which requires an approved PMA. Only absorbable dusting powders from manufacturers that have an approved PMA or NDA (before it was regulated as a device) may be used on surgeon's gloves. Powder used for lubricating examination gloves has not yet fallen under the same regulatory guidelines as those for surgical gloves.

Patient Examination Gloves

Patient examination gloves were classified as Class I medical devices in the October 21, 1980 *Federal Register* under 21 CDR 880.6250 and amended in the January 13, 1989 *Federal Register. The* amendment revoked the Premarket Notification 5 10(k) and Good manufacturing Practices (GMP) exemptions previously designated for examination gloves.

The description for patient examination gloves made of natural rubber, vinyl, or other materials given in regulation 880.6250 define the patient examination glove as "... a disposable device intended for medical purposes that is worn on the examiner's hand or finger to prevent contamination between patient and examiner."

Powder used for lubricating examination gloves should meet the USP monograph for absorbable dusting powder or be shown to be equivalent in terms of safety and effectiveness. The 510 (k) must state the type, specifications and source of powder or other dusting lubricant used on the gloves. ASTM is currently developing the Standard Test Method for Residual Powder on Medical Gloves (D 6124-97). The standard does not include a weight limit for the total powders on powder-free medical gloves.

Quality System Regulation

FDA published, in the Federal Register (FR) on October 7, 1996, a revised GMP or Quality Systems (QS) regulation which contains requirements on the control of naturally occurring material on medical devices such as adverse protein on gloves.

The new QS regulation has several revised definitions, such as the definition for manufacturing materials in §820.3(p) which is:

> "Manufacturing material means any material or substance used in or used to facilitate the manufacturing process, a concomitant constituent, or a byproduct constituent produced during the manufacturing process, which is present in or on the finished device as a residue or impurity not by design or intent of the manufacturer."

A concomitant constituent is an ingredient that naturally exists in a component of a medical device or that exists in a manufacturing material used in, or used to facilitate, the manufacturing process. The allergenic or adverse proteins that naturally occur in the natural rubber latex component of medical devices are concomitant constituents.

Specific requirements for the use and removal of manufacturing materials are in §820.70 Process Controls where @20.70(h) states:

> "Manufacturing material. Where a manufacturing material could reasonably be expected to have an adverse effect on product quality, the manufacturer shall establish and maintain procedures for the use and removal of such manufacturing material to ensure that it is removed or limited to an amount that does not adversely affect the device's quality. The removal or reduction of such manufacturing material shall be documented."

Thus, to meet direct health care concerns and to meet GMP requirements, water-soluble proteins on medical devices have to be limited by manufacturers when such proteins can be expected to have an adverse effect on patients and users.

Authors: Terrell Cunningham, Andrew Lowery

Appendix B

Adverse Health Effects

I. Biological Reactions

Glove dusting powder is composed of particles and there are predictable biological reactions to particles. The bulk of the glove powder is cornstarch, which is a resorbable particle and reactions are expected to be minimal and of short duration. This section reviews the nature of the biological reactions and the available information on these reactions to glove powder.

General Reports

A review article appearing in the peer reviewed literature in 1990, provides background information and an excellent summary of the problems associated with the use of glove powder (1). Powders have been demonstrated to cause inflammation and granulomas but a much higher dose of cornstarch is needed compared to talc. This study also cites a number of other substances such as suture material, gauze fluff, and cellulose that may cause these biological reactions more frequently than does

cornstarch which is the major particulate component of glove powder. Studies on changes in starch processing were also examined and autoclaved starch is rapidly resorbed (48 hrs. in rat peritoneum) and irradiated starch was still present at 70 days. Studies on washing the powder off were also reported and washing with saline clumps the powder rather than removing it.

There are additional general reports which do not contribute much to the discussion and do not provide recent references (2, 3). Zaza et al (4) report a good study on natural latex sensitivity with some reference to glove powder. There was no difference in sensitivity incidences when the different kinds of gloves were compared. However, nurses with cosmetic sensitivity had higher incidence. The availability and widespread use of cosmetic powders with talc and with cornstarch is cited and is an important issue in evaluating the risks associated with glove powder.

Contamination of Surgical Wounds and Peritoneal Adhesions

Contamination of surgical wounds and peritoneal adhesions are the biological reactions most frequently cited in the literature. There were pleas for powder-free gloves (5, 6) and indications that glove powder does contaminate the wounds since washing of gloves is ineffective (6).

The issue of peritoneal adhesions from the use of powdered surgical gloves is the major issue in the literature and most of these studies arc from Europe (11-12). The studies ate well documented, and the assumption is that the glove powder is cornstarch and not talc. But this is not really proven in all cases. Peritoneal adhesions following surgery are a major complication with estimates that 60–80% of intestinal obstructions are due to adhesions. The presence of foreign bodies is a major cause of these adhesions and the reactions are likely to be to sutures. However, the overall recommendation is to keep foreign bodies out of the operative area and this includes glove powder. Powder-free gloves are recommended and some available gloves or methodologies for preparing gloves are provided.

One European study had some interesting data and is the only study to have numbers that reflect incidence of reactions to glove powder (10). In 1991-1993, 448 patients were evaluated and peritoneal granulomas were found in 26% of the patients. There were suture granulomas in 25% of the patients and the surgeons of 309 patients used powdered gloves. Of these, 14 (5%) had documented starch granulomas. The overall conclusions were: the more operations on a patient; the more likely granulomas would appear. These are related to foreign bodies with sutures being the major cause. However, they do advocate avoiding depositing glove powder into the wound.

Experimental Studies

Some very interesting animal studies, mostly done in Europe, examined glove powder. The overall conclusions can be summarized that glove powder consists of particles and there is a biological response to those particles. The presence of a foreign body increases the risk of infection and cornstarch is a foreign body. However, of all the foreign bodies studied, cornstarch promotes the least

reaction (13-16).

Other Concerns with Glove Powder

There are miscellaneous reports of glove powder being left behind on devices or instruments (17, 18).

When this literature survey began, it was anticipated that pulmonary complications and associated granulomas would be the major issue. This does not appear in the literature and pulmonary complications in patients are not described.

Powder and cancer

Chronic inflammatory responses are of amcem and there is some continuing thought, but no evidence, that a site of chronic inflammatory responses may be more prone to developing a cancer. In addition, there is always the concern of foreign body carcinomas (19) demonstrated in rodents. The biggest issue with granulomas from the chronic inflammatory response is that they mimic cancers and there may be a misdiagnosis. There is no evidence of genotoxicity, mutagenicity, or carcinogenicity with cornstarch. Granulomas may mimic carcinomas and biopsies may be necessary for decisionmaking (7).

General Issues with Cornstarch

Cornstarch is a powder of particles and as such, the reactions are as those expected to particles. However, since cornstarch is a biodegradable particle, chronic responses are rare. Any modification of cornstarch that prolongs its degradationwill increase the magnitude of the reactions. Any contamination with talc will greatly increase the biological reactions. Cornstarch is a common substance in every day life. Powders and cosmetic products with cornstarch are available over-the-counter (OTC) in all stores. In addition cornstarch is common in baking and cooking. There are numerous reports of reactions to powders in cosmetics and in the work place that are not associated with health care (20, 21).

Bioburden and Powder

The issue of the level of micro-organisms on non-sterile medical gloves has been raised under various circumstances. The only study available on bioburden is an ongoing FDA funded study. Progress reports indicate organisms of pathogenic potential were found onexamination gloves in some instances. However, the issue of powder should be kept separate from the bioburden since there is no evidence that bioburden and pow&r are related.

Surgeons gloves are sterilized and thus, there is no remaining living bioburden on the finished product. Surgeons gloves, which are often highly powdered for ease in donning over wet hands, are routinely washed prior to use and the methods of washing and the effectiveness of the procedure are not well described and remain an area of concern for powder and bioburden from washing contamination._

Powder Free Gloves

Articles on the availability and suitabiity of powder-f&e gloves appeared with pleas to surgeons to use them (22, 23).

Review of Biological Reactions to Powdered Gloves

1. The use of cornstarch rather than talc for powdering gloves greatly reduced the formation of granulomas in surgical patients. Experimental studies in animals (mice, rats, rabbits) clearly point out that talc is a potent stimulator of granulomas. Experimental studies in the same animal models showed cornstarch did not stimulate granulomas. However, if the cornstarch was not resorbed it could stimulate granulomas and some of this was associated with irradiation rather than autoclave sterilization of the cornstarch. It is also apparent that contamination of glove powder with nonresorbable particulates will cause increased formation of granulomas.

2. Granulomas to particles from starch coated gloves were &scribed early. There are few granulomas &scribed in the current literature. However, adhesions of peritoneal tissue after surgery is associated with foreign bodies and remains a concern. Glove pow&r is implicated in these reactions. Proof is fairly substantial with some pathology sections which appear to be agglomerated cornstarch, however, sutures are a more common cause.

3. The studies on peritoneal adhesions clearly recommend the use of powder-free gloves.

4. The summary reviews on the hazards of powdered gloves, with the exception of adhesions, do not have recent (after mid 1980's) problems. They demonstrate the incidence of reactions to glove powder has diminished since elimination of talc and may still be declining.

5. Most of the literature comes from Europe.

6. Washing of gloves does not completely remove the powder and may cause clumping and &lay resorption of the glove powder.

7. All of these reports are based on surgical gloves since they are used on patients with whom follow-up is routine and problems would be noted.

8. Cornstarch is the major component of glove powder and is a commonpowderusedinavariety of occupations. (The bottles of talc and cornstarch that are OTC as baby powder have instructions "do not inhale." Pulmonary reactions to baby powder are documented. There are some peritoneal reactions to OTC powder used in the genital areas.)

Author: Katharine Merritt

II. Prevalence and health impact of Type I allergy to natural rubber latex (NRL)

Millions of health care workers, including groups such as physicians, nurses, respiratory technicians, and phlebotomists, use NRL gloves on a daily basis. The advent of universal precautions policies dramatically altered tk usage of NRL gloves by the health care workers. Prior to universal precautions, gloves were only employed in instances when the patient was known to be infected with a given infectious agent, such as the hepatitis B virus. A multi-state study by Kaczmareket al (24) found 100% compliance with universal precautions policies by the health care facilities in the study. Actual observed compliance by health care workers during routine procedures that could involve contact with patient body fluids was substantial, but not universal, ranging up to 92% during arterial blood gas procedures. Although many &vices employed in the health cam environment include natural latex, it is clear that NRL gloves are a crucial source of exposure to natural latex allergens for many health care workers.

Health care workers are recognized as comprising a high-risk group for natural latex allergy. Every study of health care workers has demonstrated an appreciable prevalence of natural latex sensitization as evidenced by natural latex-specific IgE antibodies and/or positive skin tests for natural latex allergy. For example, a study by Kibby and Akl (25) reported that 8.2% of hospital employees were skin test positive for natural latex reagent and 6.7% of them had class II or higher ELISAs for natural latex–specific IgE antibodies. A national+ multi-center study by Kaczmareket al (26) found that 5.5% of health care workers had natural latex-specific IgE antibodies. Nine point nine percent of the natural latex skin prick tests of 101 physicians were positive in a study by Arellano and colleagues. (27) Operating room nurses have also been studied. A study by Lagier et al (28) reported a prevalence of 10.7% natural latex skin prick test positivity among 197 operating room nurses. Finally, in a study that included dental personnel with hospital employees, Yassin et al (29) observed a prevalence of natural latex skin prick test positivity of 17%.

The general population is exposed to natural latex from a variety of sources, including consumer products such as natural latex balloons, as well as medical devices such as barrier contraceptives and the NRL gloves of health care providers, e.g., dental personnel. The prevalence of natural latex allergy among the general population has been estimated to range between 1% and 6%, lower than the corresponding range for health care workers. The upper end of the range is based on a study of blood donors in southeastern Michigan (30). This study has been questioned because blood donors may not be fully representative of the general population There is a consensus that further study is warranted.

The CDRH Epidemiology Team is currently conducting a seroprevalence study of natural latex-specific IgE antibodies among NHANES (National Health and Nutrition Examination Survey) III participants. This study, with an estimated sample size of several thousand individuals, will substantially increase the understanding of the epidemiology of natural latex allergy among the general population

Author: Ron Kaczmarek

III. Role of glove powder in allergic reactions to natural rubber latex (NRL)

Clinical studies

A number of publications since the mid 1980's, reported respiratory problems and asthma like attacks in hospital employees and patients. The problem was ascribed to inhalation of airborne natural latex allergen in the areas of heavy use of powdered gloves (31-39). Affected individuals were frequent users of medical gloves, mainly nurses and physicians. The reactions to airborne natural latex allergens were also reported in other occupationally exposed individuals (38, 40) and/or environmentally exposed individuals (35). It is estimated that roughly 30% of natural latex sensitive individuals develop respiratory problems (31), and that aerosolized glove powder in areas of frequent glove use may affect direct users as well as those who do not use natural latex products, but are in the same areas (41). Furthermore, a recent study from Finland demonstrated a rather low prevalence of respiratory allergy reactions in one hospital, in which pow&r-free gloves were used for an extended period of time (42). The conclusions regarding the role of glove pow&r in the above clinical reports were based onmedical histories of individuals presenting symptoms, on positive skin tests and, in some cases, on positive inhalation test.

Binding of natural latex proteins to cornstarch powder

The propensity of cornstarch to bind natural latex proteins was studied in &tail in two recent publications. Three preparations of cornstarch a) clean, unused dusting pow&r, b) cornstarch exposed to natural latex protein extracts and c) cornstarch extracted from powdered gloves, were evaluated for total protein levels (43) and for allergenic protein levels (43, 44). Unexposed cornstarch contained no allergenic proteins, while both natural latex exposed cornstarch preparations had a significant amount of allergenic proteins bound to the particles. The results of both studies clearly demonstrate that cornstarch indeed binds allergenic proteins, which can not be detached by simply washing the powder. These findings support the causal relationship between asthmatic reactions in individuals with natural latex allergy and the exposure to airborne particles from NRL products.

Airborne dove powder as an allergen carrier

Several papers describe measurements of airborne particle levels in the environment with frequent use of NRL gloves. Airborne particles were collected through filters and analyzed for allergen content.

Airborne natural latex allergen levels were evaluated in the laborataies using either powdered gloves or powder-free gloves (45). This study showed much higher allergen levels ranging from 39-311 ng/m^3 in laboratories where powdered gloves were used in comparison with the levels of less than 20 ng/m^3 in laboratories where powder-free gloves were used. More &tailed measurements of the airborne allergen were done in the operating rooms, comparing airborne allergen levels on days when high-allergen gloves were used with days when low-allergen gloves were used and finally with no surgery days (46). The median allergen level of 13.7 ng/m^3 on high-allergen glove days was down to 1 ng/m^3 and 0.6 ng/m^3 on low allergen glove days or no surgery days, respectively. In the environment where powdered gloves were used, large quantities of allergen could also be collected from personnel lab coats and scrub suits (47).

These studies demonstrate that the level of airborne allergen is directly related to the frequency of powdered glove usage in particular areas and to the level of allergen/powder on the gloves used.

Respiratory problems in natural latex allergic individuals

A number of published papers provide direct evidence that natural latex protein allergens, bound to corn starch particles are a cause of respiratory allergic reactions and asthma like attacks. This has been d-ted by the bronchial provocation test, performed by exposing allergic individuals to inhalation from powders on NRL gloves. A change in the Forced Expiration Volume (FEV), a measure of pulmonary function, is an indication of intensity of the reaction to allergen.

Patients who developed rhinitis, conjunctivitis and dyspnea when in the operating room theater or in other hospital environments with a heavy use of NRL gloves, were evaluated for natural latex allergy (medical history, specific IgE antibodies, skin test). After positive diagnosis of existing allergy to natural latex proteins, patients underwent the bronchial provocation test with airborne powder particles from NRL gloves. Test subjects were asked to handle powdered NRL gloves and powdered non-NRL gloves while their respiratory functions were monitored. They could handle up to 20 pairs of non-NRL gloves inhaling the powder particles, without any respiratory symptoms, while the same individuals, after handling as few as one pair of NRL gloves started to develop airway resistance (48). Furthermore, the preparation of glove pow&r from NRL gloves tested by bronchial provocation test and skin test, demonstrated positive reactions in both cases (49). In another study, a provocation test with clean cornstarch that has not been in the contact with a natural latex product did not provoke any respiratory reaction, while in the same individuals, powder from NRL induced asthmatic reaction (50). The control individuals with no natural latex allergy, did not develop any symptoms during provocation with allergenic powder.

In a more recent well controlled study (51), the bronchial provocation test was performed with the extracts from powder-free surgical gloves, from powdered surgical gloves and with a clean cornstarch powder extract. A clean cornstarch powder caused no bronchial reaction in sensitized subjects. Exposure to a nebulized powder-k NRL surgical glove extract induced immediate bronchoconstriction in two of four tested subjects. However, when nebulized powdered glove extract was tested, a 1: 10 dilution of the extract induced bronchoconstriction in all four tested subjects and the intensity of the reaction was the same as with undiluted powder-free glove extract.

A recent study from Belgium (52) revealed that 4.7% of hospital personnel were allergic to natural latex, confirmed by medical history and skin testing. Allergic individuals were pretested for bronchial responsiveness and then exposed to the provocation test with powdered NRL gloves. A total of 58% of allergic participants or 2.6% of the entire surveyed population developed an asthmatic reaction, while the provocation with vinyl glove powder did not cause any change in bronchial functions.

In summary, the studies reviewed above lend support to the conclusion that airborne glove powder may represent a threat to individuals allergic to natural latex proteins. Avoidance of use of natural latex products by such individuals may provide insufficient protection from natural latex proteins if they are in the environment of powdered glove use. Since there is not current safe and effective therapy for natural latex allergy, avoidance of all sources of natural latex allergen is the only available therapeutic option.

Role of glove powder in irritation and contact dermatitis development

Another issue that has to be addressed is a possible causal relationship of glove powder with the irritation and contact dermatitis development.

It is known that cornstarch used for donning is a strong absorbii powder and has a tendency to cause dryness of the skin leading to cracking and itching. A compromised epithelium can have serious health

c&sequences. Not only that barrier properties for infectious agents are reduced, but also in this case, chemicals used in the production of NRL gloves and natural latex proteins can penetrate a damaged skin enhancing chances of development of both Type IV and Type I allergy. Skin reactions to glove pow&r have been observed and interpreted as irritant reactions (53). The major factors influencing elicitation of irritant dermatitis are dose and exposure time, and termination of exposure is the cure. Therefore, in the case of NRL gloves, a prolonged contact with glove powder may have serious impact on the user skin condition.

There are no data that directly implicate cornstarch powder as a cause of allergic contact dermatitis up to now. However, it has been reported that nonimmune proinflammatory agents can augment the response to contact sensitizers (54). This augmentation occurs with subthreshold doses of both irritants and allergens and therefore, individuals that may have not presented symptoms of either reaction, can still react in case of a combined exposure (55).

These published data (although limited) and clinical experience implicate that cornstarch powder on the NRL gloves, in addition to its role in Type I allergy, may also be a contributing factor in the development of irritation and Type IV allergy.

Author: Vesna Tomazic

IV. Medical Device Reporting (MedWatch) Database

FDA's adverse event databases rarely contain event text or coded information that would allow for comprehensive, automated tallies of reported medical glove related events. Reports cannot differentiate between events associated with either Type I or Type IV hypersensitivity reactions, including reactions to powder-free vs. powdered glove products. However, based on a review of all reports, it is possible to provide the following information summary.

As of August 27, 1997, 2,501 voluntary and mandatory incident reports involving natural rubber latex containing medical gloves have been entered into FDA's adverse event database. A review of database information indicates that approximately 1,550 or 62% of these medical glove related reports allege the occurrence of adverse events that involve allergic reactions, including anaphylaxis. The text of these reports indicate the occurrence of either skin reactions (Type IV or Type I) or systemic (type I) allergic reactions of one or more health care professionals or patients to medical gloves.

Approximately 100 or 4% of medical glove related adverse event reports allege specific glove pow&r residue complaints. These reports raise concerns regarding granuloma formation, general concerns regarding infection risk associated with powder content, low powder content making donning difficult, contamination with unidentified debris or insect parts, mold growth, and high levels of powder on gloves labeled as "powder-free." A glove powder related death report was submitted in 1986 under the procode for surgeons' gloves. The reporter, a manufacturer, indicated that a physician had questioned the role that glove powder could have played in the death of a patient who experienced post-operative peritonitis related complications.

The remaining 851 (33%) reports are primarily related to concerns regarding product barrier integrity. However, it should be noted that problems with degradation of the desirable physical properties of medical gloves has also been associated with powder-free glove manufacturing processes such as chlorination.

Author: Sharon Dillard

Appendix C

Alternatives to Glove Powder

As discussed in previous sections of this report, glove powder has been implicated in the post-operative formation of adhesions, and in some instances, in granuloma formation. Also as discussed previously, natural latex allergens bound to airborne glove powder are known to cause respiratory problems far natural latex allergic individuals. Although the use of glove powder as a dusting lubricant is very common, there are other alternatives available. This section discusses several alternatives to powdered NRL gloves.

Chlorinated natural latex rubber (NRL) gloves

Although lubrication of the NRL glove surface can be accomplished with various dusting powders, the powder can be rubbed off and become airborne during use. A more permanent method of reducing surface drag in natural rubber latex products is known as halogenation. When carried out using chlorine as the active element - as is commonly done with NRL gloves - the process is called chlorination.

Chlorination of the NRL gloves is performed by immersing the gloves in a dilute solution containing free chlorine ions. The chlorine reacts with the natural rubber surface to reduce the natural tackiness of the natural latex, hence eliminating the need to add a dusting pow&r to the glove. After immersion of the glove into the dilute chlorine solution (usually between 0.05–0.30%), the gloves are washed in water, dipped in a neutralizing solution (e.g., 1% ammonia solution), rinsed again, and then dried (56). This extra washing performed during and after chlorination greatly reduces the level of extractable latex proteins in the product. Some latex proteins are even converted to insoluble forms during chlorination itself (57).

One significant drawback to using chlorinated NRL gloves is that some of the mechanical and physical properties of the natural latex are compromised. Woods et al (58) states that the chlorination process adversely affects shelf life, grip and in-use durability of the glove. In addition, strong odors may be present in chlorinated gloves, as well as possible skin irritants.

An FDA study of the effects of elevated temperature on the tensile strength of NRL gloves showed very dramatic results for powder-free examination gloves that are believed to have been chlorinated. Various styles of NRL gloves were placed in paper envelopes and oven-aged in air for 7, 14, and 21 days at 70º Celsius, and then subjected to tensile testing per ASTM D 412. (Accelerated aging in the laboratory at 70º C is common for NRL gloves, and is one of two recommended temperatures for aging of gloves in ASTM D 3577 and ASTM D 3578.) Five of seven pow&r-free styles exhibited dramatic decreases in tensile strength after just 7-14 days at 70º C, with total decreases in tensile strength ranging from 70% to over 90% at 21 days of aging. Although the &tails of the manufacture of these five styles are proprietary, it is believed that all were chlorinated. In contrast, almost half of the pow&fed gloves subject to the same conditions showed no statistically significant decrease in tensile strength, while the remaining powdered gloves decreased a moderate 10 to 25% by 21 days of exposure (59). A progress report from an ongoing federal–state contract study on NRL exam gloves recently indicated similar results: extreme &gradation of chlorinated exam gloves observed after 14 to 21 days of aging at 70º C (60).

Slight variations in the chlorination process are known (56, 61, 62). For example, variations in solution strength, immersion time, neutralizing agents, time elapsed between chlorination and neutralization, drying temperature and drying time can all influence the effects of chlorination. Aziz (56) tested gloves chlorinated with 0.01 %, 0.03%, 0.05%, 0.1% and 0.3% chlorine solutions. For unaged samples, tensile strength was main&i& from 1 to 20 minutes of chlorination time for all samples except those chlorinated with the 0.3% solution, in which tensile strength decreased by approximately 25%. For samples aged 7 days at 70º C, original tensile strength decreased slightly for up to 20 minutes of chlorination, except for the 0.3% samples, where the tensile strength decreased by

roughly 50% for 20 min. of chlorination. For samples aged 22 hours at 100º C, original tensile strength was maintained only for the 0.01% solution. The strengths of tk remaining samples decreased 50-95% after only 2-6 minutes of chlorination.

Aziz also showed the higher concentrations of chlorine lead to microscopic cracks in the surface of the natural rubber latex. Chlorination time and solution strength also affect the color of the finished product (longer times and higher concentrations lead to a more yellow product). Thus, in order to avoid the potential negative effects of chlorination, chlorine concentrations and immersion times should be carefully chosen

Synthetic polymer linings

Another alternative to powdered gloves is a NRL glove having a synthetic polymer lining on the internal surface of the glove. The slippery surface of such a lining facilitates donuing of the glove. Synthetic polymer coatings may be made of a hydrogel, silicone, or another polymer. It appears that no shelf-life data exist to substantiate the lq-term barrier properties of synthetic polymer-coated NRL gloves.

In the case of hydrogel polymer linings, the NRL glove is dipped into a solution of the hydrogel prior to the final curing stage of glove manufacture. The hydrogel lining is physically bonded to the natural rubber latex (58) and lies on the internal skin-contacting surface of the finished product. Due to its low coefficient of friction, the hydrogel lining facilitates donuing with either wet or dry hands (63, 64, 65).

Other approaches

From the late 1800s to the mid-twentieth century, surgeons-used water as the primary lubricating agent when donning &loves. The protective rubber gloves utilized at that time were designed for multiple use, and thus were pulled onto wet hands after being "sterilized" [sic] in boii water (58, 63, 66). Water is not au effective glove lubricant for today's thin, close-fitting NRL &loves.

Glove liners in the form of cotton or nylon stretch gloves, or liners ma& of materials designed to resist puncture, are sometimes worn underneath NRL &loves, between the bare skin and the glove. Although liners are not used to facilitate donuing, they will provi& a layer of protection to the user, and thus reduce the risk of skin irritation. They also reduce discomfort due to hand sweating. Gloving creams are sometimes used to facilitate the donning of gloves and at other times, are used to reduce the wearer's potential for skin irritation. However, if used with powdered &loves, such glove liners and creams will do nothing to eliminate the occurrence of airborne natural latex allergens.

Gloves made from materials other than natural rubber latex (e.g., synthetic rubbers or other synthetic polymers) are available, but none possess the unique mix of properties (high elasticity and tensile strength, excellent film-forming characteristics) found in NRL gloves (57, 66). Gloves ma& from some of these alternative materials, such as plasticized PVC, include high levels of chemical additives which may cause skin irritation and/or allergic reactions (66, 67). Furthermore, the barrier properties of alternative glove materials must be thoroughly examined prior to their selection for use.

Summarg

Chlorination of NRL gloves is a common alternative to the use of glove powder. Chlorination has au adverse affect on various mechanical and physical glove properties, which may affect shelf-life. Thus, the chlorination process should be tightly controlled. Gloves ma& of synthetic materials are available, but none possess the unique mix of physical properties offered by natural rubber latex. Synthetic polymer-coated gloves are another possibility, but as is the case with both NRL and non-NRL &loves, it appears that little or not shelf-life data exist in the current literature to substantiate the long-term barrier properties of this type of medical glove.

Appendix D

Glove Market Availability

In 1996, the U.S. imported 20.8 billion medical gloves, 62% of which came from Malaysia. Since 1991, the number of medical gloves imported into the U.S. has increasedby 247%. See the table below provided by the Division of Small Manufacturers Assistance (DSMA).

U.S. Medical Glove imports
(in billions)

	1991	1992	1993	1994	1995	1996
Malaysia	3.9	7.6	9.9	10.4	11.8	13.0
Thailand	0.9	1.8	2.0	1.7	2.2	3.2
Indonesia	0.2	0.6	0.8	0.8	1.1	1.9
Sri Lanka	0.2	0.5	0.3	0.5	0.6	0.7
India	0.1	0.3	0.5	0.5	0.5	0.6
Taiwan	*	*	*	*	0.4	0.3
China	0.5	0.4	0.7	0.6	0.6	0.8
Others	0.2	0.2	0.3	0.4	0.2	0.3
Total Imports	6.0	11.4	14.5	14.9	17.4	20.8
% Increase		90%	27%	3%	17%	20%

*** Number of imports not enough to be included in top seven countries in this table.**

These numbers include medical gloves of all types: NRL, powder-free NRL, and non-NRL. In 1996, the distribution by type was 90% NRL and 10% non-NRL. Of the 90% natural rubber latex, 20-25% were powder-free latex and chlorinated. Only a small number of manufacturers are using a process other than chlorination to produce powder-free gloves.

Malaysia is the largest producer of natural latex worldwide. Over 90% of all patient examination gloves are ma& from natural latex, and it is estimated that up to 80% of NRL patient examination gloves consumed in the U.S. are manufactured in Malaysia (68). The Association of Malaysian Medical Industries (AMMI) represents Malaysian and multinational companies involved in the development and manufacture of medical devices, products, equipment and services in Malaysia for the health care community worldwide. The Malaysian Rubber Glove Manufacturers' Association (MRGMA) specifically represents the NRL glove manufacturers. According to the AMMI and MRGMA, any significant increase in the numbers of medical gloves available for importation is not likely. However, a shift in the types of gloves (powdered to powder-free) is already occurring.

In June 1997 as a result of the NIOSH alert, five questions regarding current and future availability of medical gloves to the U.S. were posed to the entire 20 company AMMI membership, nine of which were glove-only manufacturers, also members of MRGMA. The responses were compiled and presented to CDRH by an AMMI executive and MRGMA member at a subsequent June meeting. The questions and AMMI responses follow. Wherever appropriate, supplemental supporting documentation

is included

1. What is your current monthly and/or annual capacity for manufacturing NRL and powder-free NRL medical gloves for the U.S.?

The total capacity from Malaysia in 19% was 13 billion (including 10% non-NRL) pieces. This capacity will not change significantly. The projected Malaysian industry trend is to shift the ratio of powdered (P) to powder-free (PF) natural rubber latex. AMMI and MRGMA project this shift to be rapid as indicated below.

	P to PF Latex
12 months ago	80:20
6 months ago	75:25
today (June 1997)	65:35
12 months from now	50:50

2. How do these numbers compare to distribution outside the U.S.?

The ratio of Malaysian medical gloves for U.S. distribution to the rest of the world is 70:30. Partly due to volume and purchasing requirements, other countries are more willing to pay the higher prices of powder-free NRL gloves. As a comparison to the P to PF ratio above, the ratio in the United Kingdom is:

	P to PF Latex
3 months ago	75:25
today (June 1997)	55:45
12 months from now	40:60

3. If there was a request by the U.S. health care community to produce a larger quantity of powder-fke medical gloves, how quickly could this increase occur and by what percent?

If the U.S. health care community couldbear the "current market price" of gloves, the powder-free glove supply to other parts of the world could be significantly shifted to the U.S. Demand for powdered gloves has already dropped worldwide. One constraint to any possible shift is long-term contracts. Half or 50% of glove manufacturers have long-term contracts that stretch 6-12 months. Unless the U.S. price warranted, these contracts would not be re-negotiated.

The lines producing powder-free NRL gloves are currently working to capacity. Conversion of lines is expensive and requires 12-18 months before realizing an increased capacity. Some of the obstacles include acquiring chlorinators, which are backlogged worldwide, and water treatment enhancements. It is doubtful that the industrial process would shift to greater than 60% powder-free vs. 40% powdered NRL. Any greater erosion from powdered would be ma& up by a shift to non-NRL. Ten percent of the current Malaysian market is non-NRL and is growing. Although non-latex technology is not yet equal to that of natural rubber latex, glove manufacturers are attempting to perfect the nonlatex process and anticipate future increases in the nonlatex market.

However, additional FDA staff research found tbat non-NRL gloves, other than vinyl, are considerably more expensive than NRL gloves.

Glove Prices to Hospitals (69)

(in U.S. dollars per box of 100 pieces)

Exam	Vinyl	Natural Rubber Latex (NRL)	Synthetic Rubber	Synthetic Polymer
Powdered	3.50	3.90	8.00	12.00
Powder-free	4.20	5.80	10.00	15.00
% of Increase for Powder-free Product	20%	49%	25%	25%

For the powdered gloves, NRL costs are 11.4% higher than vinyl but synthetic rubber is 128.5% higher than vinyl and 105% higher than NRL. For powder-free gloves, NRL costs are 39% higher than vinyl but synthetic rubber is 138% higher than vinyl and 72.4% higher than NRL. Moving to a synthetic glove is currently cost prohibitive for U.S. hospitals.

Although vinyl gloves are less expensive than NRL, research indicates they are not necessarily the best alternative. Both NRL and vinyl patient examination gloves provide protection against microorganisms; however, it has been demonstrated that NRL is preferred to vinyl for more effective and durable barrier qualities (70, 71). NRL is pliable allowing for natural molding for more appropriate fit and has the abiity to reseal when tiny punctures occur. In general, NRL provides comfort to the wearer, adequately protects against microorganisms, and provides adequate barrier effectiveness when used for medical and nursing procedures (70). Consequently, NRL is still the barrier of choice in the U.S.

4. Would an increased volume impact importation/distribution to the U.S.? If so, what obstacles may youencounter?

   U.S. entry requirements can be a problem for glove manufacturers which result in delays and, in some cases, a barrier too costly to pursue. Some specific obstacles which act as a deterrent are:

   - 510(k) requirement of biocompatibility testing. There are very few laboratories available to conduct the testing causing a current 2-4 month backlog. It would be helpful if a "contingent" 510(k) approval could be granted while biocumpatibility testing is being conducted. This would allow the manufacturer the opporhmity to recoup some of the start-up expenses. It is cost prohibitive for a manufacturer to maintain the facility without any return, even for a relatively short period of time.
   - 510(k) processing time. The current 90 days is all the manufacturers can afford. It would be an obstacle if an increase in 5 10(k) applications would cause a backlog.
   - Regulatory expenses. Other countries are offering prices comparable or greater than those offered by the U.S. To avoid U.S. regulatory expenses/hassles, glove manufacturers are strongly inclined to direct their products tomarkets they can enter without &lay or added costs.

5. What would be your special concerns and/or difficulties producing a larger quantity of powder-free NRL medical gloves, if any?

   Barrier integrity is the main concern for medical gloves and glove manufacturers. Producing a product that will consistently meet water leak tests is of special concern However, the current anxiety over natural latex allergy is resulting in a shift to materials and/or processes that may compromise barrier integrity. In a shortage situation, or even a perceived shortage situation,

inconsistent quality suppliers may seize the opportunity to move into the U.S. market. This will result in poor barrier products entering the U.S., much as they did in 1988-89 when demand rapidly increased because of concern regarding universal precautions.

Producing a product tbat will have acceptable shelf life (one-year) is another special concern and/or difficulty. Powder-free technology is not easy and chlorination contributes to the difficulty. Most powder-free gloves are chlorinated and suppliers of auxiliary equipment are already back-ordered at least six months. However, chlorination is not the only process for producing powder-free NRL gloves. More emphasis needs to be placed on other processes which may help improve shelf life.

In summary and based on additional investigation, comprehensive labeling, including warnings and precautions, added to all medical NRL gloves would not be significant. The health care community is largely aware of natural latex allergenicity and has been making appropriate adjustments. The demand for more powder-&e or lower protein gloves will most likely increase, and as refinement in other manufacturing processes improve and lower protein NRL is developed, the shift will be toward medical gloves other than chlorinated powder-free.

Author: Carol Herman

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CDRH Glove Powder Working Group:

Terrell Cunninghan	CDRH	ODE
Sharon Dillard	CDRH	OSB
John Farnham	CDRH	OC
Carol Herman	CDRH	OSB
Delon Hull	NIOSH	
Ron Kaczmarek	CDRH	OSB
Chiu Lin	CDRH	ODE
Andrew Lowery	CDRH	OHIP
Katharine Merritt	CDRH	OST
John Stigi	CDRH	OHIP
Mel Stratmeyer	CDRH	OST
Vesna Tomazic	CDRH	OST
Donna Walsh	CDRH	OST

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COMMENTS

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